

## Supramolecular Spheres Self-Assembled from Conical Dendrons Are Chiral

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## S Supporting Information

**ABSTRACT:** Frank–Kasper phases and liquid quasicrystals self-organize from supramolecular spheres of dendrimers, block copolymers, surfactants and other self-assembling molecules. These spheres are expected to be achiral due to their isotropic shape. Nevertheless, supramolecular spheres from short helical stacks of crown-like dendrimers self-organize a  $Pm\bar{3}n$  cubic (Frank–Kasper A15) phase which exhibits chirality on the macroscopic scale. However, the chirality of classic isotropic supramolecular micellar-like spheres, generated from conical dendrons, is unknown. Here we report a library of second and third generation biphenylpropyl dendrons with chiral groups at their apex that produces single-handed chiral supramolecular spheres. Up to 480 conical dendrons self-assemble to form micellar-like spheres, with a molar mass of up to  $1.1 \times 10^6$  g/mol, that self-organize into a  $Pm\bar{3}n$  phase with chirality detectable on the macroscopic scale. This demonstration of chirality in micellar-like spheres of a Frank–Kasper phase raises the fundamental question whether micellar-like spheres forming 3D phases generated from other soft matter such as block copolymers, surfactants, and other molecules are chiral.

Since their introduction by Frank and Kasper in 1958 to describe the structure of metal alloys,<sup>1</sup> Frank–Kasper phases have been demonstrated to be more widely relevant, and were discovered for self-assembling dendrimers via generational<sup>2</sup> and deconstruction approach<sup>3</sup> libraries, for block copolymers,<sup>4</sup> surfactants,<sup>5</sup> lipids including glycolipids,<sup>6</sup> and others.<sup>7</sup> Common to all Frank–Kasper phases observed from soft matter, including  $Pm\bar{3}n$  (known also as A15) cubic,<sup>2d–f</sup>  $P4_2/mnm$  tetragonal (known also as  $\sigma$ -phase),<sup>2g</sup> C14 and C15 Laves phases,<sup>4f,g,5c</sup> and related dodecahedral liquid quasicrystals,<sup>2h</sup> are supramolecular spheres which are energetically<sup>8</sup> and entropically<sup>9</sup> favored.

Canonically spheres are inherently achiral. However, a helical path drawn on the surface of a sphere, known as *loxodrome*<sup>10</sup> or, to master mariners, *rhumb line*, exhibits chirality.<sup>11</sup> This spherical helix is easily manifested on the macroscopic scale by a helical apple peel.<sup>12</sup> On the

supramolecular scale chiral spheres have been self-assembled from crown-like dendrimers that generate short helical columnar stacks of molecules.<sup>13</sup> The periphery of these crowns fills space to generate supramolecular spheres. The helicity and thus chirality of such spheres arises from the chiral columnar core, which is anisotropic.<sup>14a</sup> Chirality in hollow supramolecular spheres of truncated cons of dendritic dipeptides in solution also arose from a chiral helix forming the hollow core of the spherical assembly.<sup>14</sup> However, spherical chirality from isotropic micellar-like spheres generated from conical dendrons has not been demonstrated.

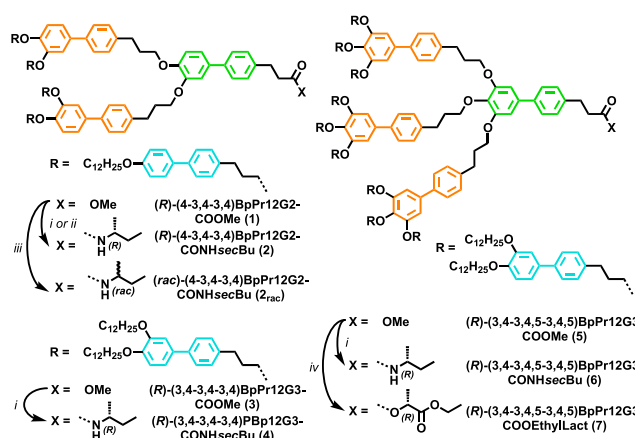
Spheres self-assembled from biphenylpropyl ether dendrons with ester and alcohol groups at apex self-organize into  $Pm\bar{3}n$  phases.<sup>2c</sup> These spheres are micellar-like because the constituent dendrons adopt a conical conformation, akin to that generated by amphiphilic block copolymers or surfactants when packing into micelles.<sup>4f,g,5c</sup> Inspired by studies which demonstrated that the handedness of the chirality of a supramolecular object can be selected by a homochiral moiety,<sup>2a,b</sup> a library of nine second and third generation biphenylpropyl ether dendrons with chiral or racemic ester and amide groups at the apex was synthesized (Scheme 1), five of which are discussed below.

The biphenylpropyl ether dendrons with methyl esters at the apex (**1**, **3**, and **5**) were synthesized and analyzed by X-ray diffraction (XRD), molecular modeling and reconstructed electron density maps,<sup>2c</sup> TEM,<sup>2a,b,e</sup> isomorphic replacement,<sup>2a,b,i</sup> and AFM.<sup>2a,b,f</sup> Dendron methyl esters **1**, **3**, and **5** were first hydrolyzed with KOH in refluxing ethanol, and then converted to acyl chlorides by treatment with  $\text{SOCl}_2$  and catalytic DMF in  $\text{CH}_2\text{Cl}_2$ . Subsequent amidation of the acyl chlorides with (*R*)-*sec*-butylamine gave biphenylpropyl dendrons with chiral amide groups at apex (**2**, **4**, and **6**) after column chromatography and precipitation of  $\text{CH}_2\text{Cl}_2$  solution into methanol. Dendron amide **2** and its racemic analogue **2<sub>rac</sub>** were also synthesized via 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) and *N*-methylmorpholine (NMM) coupling with the acid dendron and (*R*)-*sec*-butylamine for **2** or racemic *sec*-butylamine for **2<sub>rac</sub>** both in  $\text{CHCl}_3$ . A third generation dendron with a chiral ester group at apex<sup>2f</sup> was prepared via Mitsunobu

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Scheme 1. Synthesis of Conical Biphenylpropyl Dendrons with Chiral or Racemic Amides or Esters at their Apex<sup>a</sup>

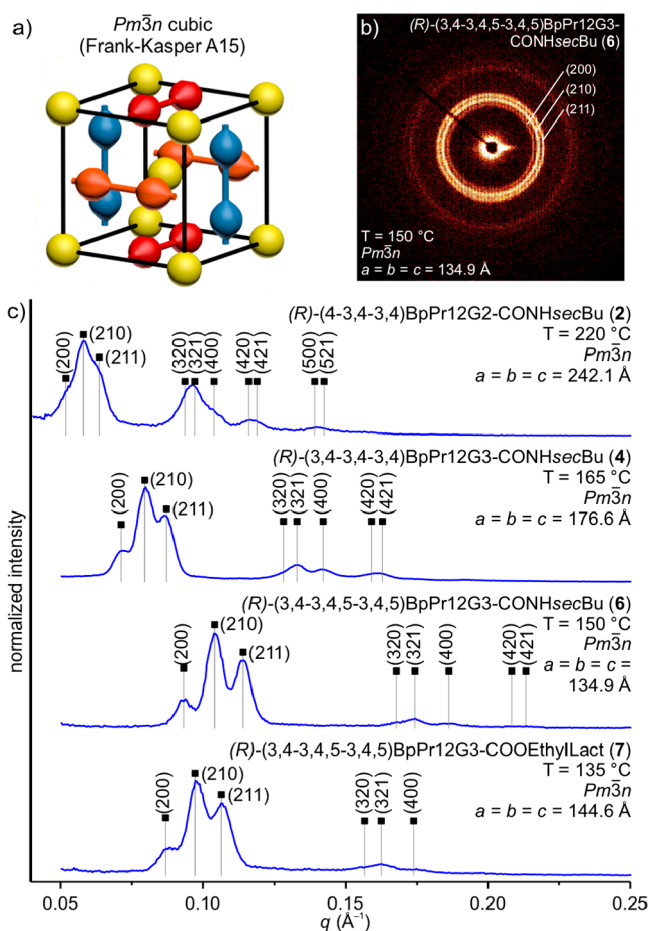
<sup>a</sup>Reagents and conditions: (i) KOH, THF, EtOH, reflux, 12 h; then SOCl<sub>2</sub>, DTBMP, cat. DMF, CH<sub>2</sub>Cl<sub>2</sub>, 23 °C, 2 h; then (*R*)-*sec*-butylamine, CH<sub>2</sub>Cl<sub>2</sub>, 23 °C, 15 h; (ii) KOH, THF, water, reflux, 2 h; AcOH; then CDMT, NMM, (*R*)-*sec*-butylamine, CHCl<sub>3</sub>, 0 to 23 °C, 12 h; (iii) KOH, THF, water, reflux, 2 h; AcOH; then CDMT, NMM, *sec*-butylamine, CHCl<sub>3</sub>, 0 to 23 °C, 12 h; (iv) KOH, THF, EtOH, reflux, 12 h; then PPh<sub>3</sub>, DIAD, (*R*)-ethyl lactate, THF, 23 °C, 8 h.

reaction of the acid dendron derived from 5 with (*R*)-ethyl lactate in THF.

Analysis of 2, 4, 6, and 7 by differential scanning calorimetry (DSC) (Figure S1) demonstrated self-assembly into thermotropic phases, which were determined by XRD (Figure 1). Second generation dendron 2 assembles into a smectic phase only upon first heating below 74 °C and a columnar hexagonal ( $\Phi_h$ ) 2D array which transforms into a cubic  $Pm\bar{3}n$  phase upon heating above 147 °C (Figure 1a). Subsequent heating and cooling recover only the  $\Phi_h$  and phases. No  $\Phi_h$  array was observed for third generation dendrons 4, 6, and 7, which exhibit only  $Pm\bar{3}n$  phases below isotropization (at 192, 155, and 145 °C, respectively).

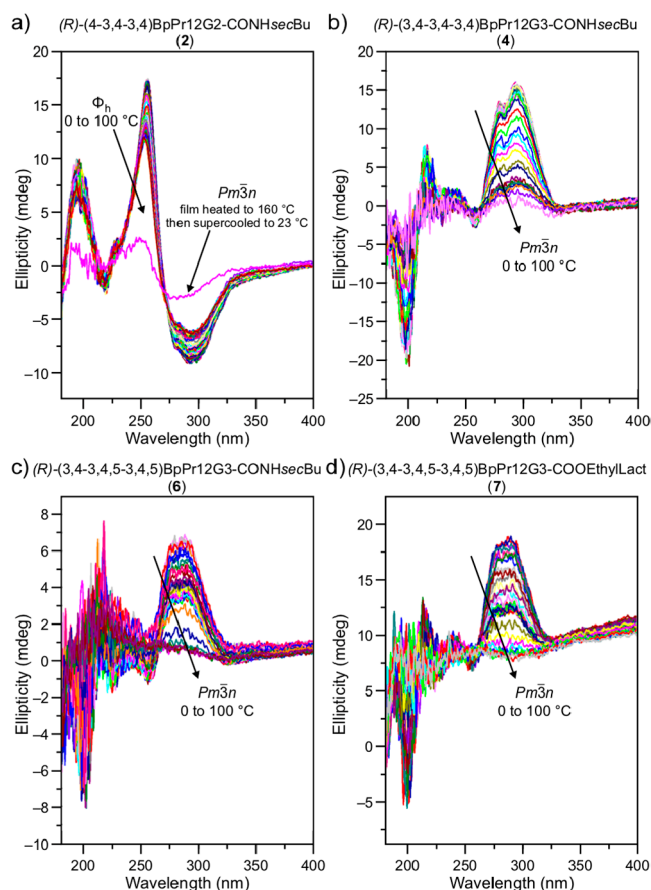
Second generation dendron 2 self-organizes into a  $Pm\bar{3}n$  phase characterized by unit cell dimensions  $a = b = c = 242.1$  Å, that in agreement with the corresponding ester, is made of hollow spheres (Figure 1c, top XRD, to be compared with Figures 6, 7, 8, and 9 in ref 2c).<sup>2c</sup> This unit cell is larger than those self-organized from third generation dendrons 4, 6, and 7 ( $a = 176.6$ , 134.9, and 144.6 Å, respectively) (Figure 1c and Table S1).

The unit cell of the  $Pm\bar{3}n$  lattice contains eight supramolecular spheres (Figure 1a). Retrostructural analysis considering the density of the dendrons ( $\rho = 1.03$  g/cm<sup>3</sup> for 2 and 1.01 g/cm<sup>3</sup> for 4, 6, and 7) indicates that the average number of molecules in a single supramolecular sphere of 2, 4, 6, and 7 is 480, 140, 30, and 37 molecules, respectively (Table S2). The 480 molecules in a single sphere of 2 correspond to a molar mass of  $1.1 \times 10^6$  g/mol, providing an example of a supramolecular dendrimer with an ultrahigh molecular weight ( $MW \geq 1.0 \times 10^6$  g/mol).<sup>2c</sup> Racemic dendron 2<sub>rac</sub> and chiral dendron 2 display identical DSC and XRD patterns, which demonstrate identical structures except that 2 is single handed. It is not known at this time if the racemic lattice contains mixtures of left and right handed homochiral spheres or racemic spheres containing helix inversion within the same structure. Circular dichroism (CD) on thin films of 2, 4, 6, and



**Figure 1.** XRD patterns of the  $Pm\bar{3}n$  phase self-organized from conical dendrons with chiral groups at the apex 2, 4, 6, and 7. (a) Schematic of the  $Pm\bar{3}n$  unit cell. (b) Fiber XRD pattern of 6. (c) Powder plots of intensity versus  $q$  taken from fiber XRD of 2, 4, 6, and 7.

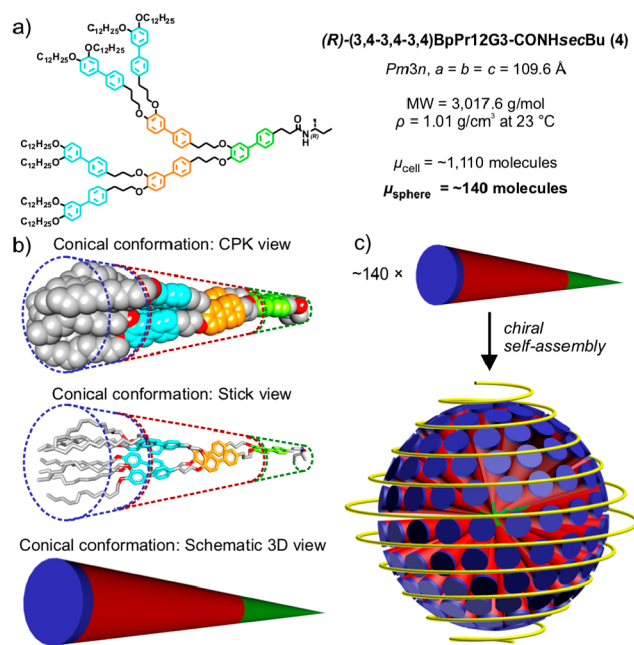
7 was used to analyze their chiral assembly in the bulk state. Thin films were prepared by spin-coating a CHCl<sub>3</sub> solution of the dendron onto a quartz plate. All films were tested to verify the absence of linear dichroism (Figure S2). All four dendrons exhibit CD ellipticity in bulk state between 0 and 100 °C (Figure 2). Second generation dendron 2 self-organizes into a  $\Phi_h$  phase below 147 °C. Hence CD measurements between 0 and 100 °C (the limit of our instrument) arises from helicity in supramolecular columns generated by the  $\Phi_h$  phase of 2 (Figure 2a). Separately heating a thin film of 2 to 160 °C and then supercooling to 23 °C enabled the  $Pm\bar{3}n$  phase to be kinetically trapped. A CD measurement of this quenched thin film (pink line in Figure 2a) demonstrates that chirality persists in the  $Pm\bar{3}n$  phase of 2 and hence its constituent supramolecular spheres are chiral. The chirality of the supramolecular spheres in the  $Pm\bar{3}n$  phase is further demonstrated by variable temperature CD of thin films of 4, 6, and 7 (Figure 2b–d). These three dendrons self-organize into only  $Pm\bar{3}n$  phases below their isotropization temperatures, which are all higher than 100 °C. Hence CD of their thin films directly measures chirality in their  $Pm\bar{3}n$  arrays. Figure 2b–d demonstrates that these cubic arrays exhibit supramolecular chirality, which must arise from helicity in their constituent supramolecular spheres. The Cotton effect in Figure 2b–d shows a positive exciton coupling, suggesting that the spherical



**Figure 2.** Chiral self-organization of conical dendrons with chiral groups at the apex in the  $Pm\bar{3}n$  phase. Temperature dependence of the thin film CD spectra of the  $Pm\bar{3}n$  lattice self-organized from conical dendrons upon heating from 0 to 100 °C: (a) 2, (b) 4, (c) 6, (d) 7. In panel a, a thin film of 2 was also heated to 160 °C and supercooled to 23 °C to measure the  $Pm\bar{3}n$  phase (pink line). Thin films were prepared on a quartz plate by spin-coating a  $\text{CHCl}_3$  solution of the dendron (2, 1.1% w/v; 4, 1.2% w/v; 6, 0.8% w/v; 7, 0.9% w/v). No linear dichroism was detected.

helicity of 4, 6, and 7 is right-handed.<sup>15</sup> This Cotton effect arises in the spectral window of the aromatic biphenylpropyl portions of the dendrons, demonstrating that chiral information is transferred from the chiral group at the apex of the dendron to the periphery of the aromatic part of the supramolecular sphere. The intensity of the CD signal decreases with increasing temperature for 4, 6, and 7 due to increased molecular disorder and helix unwinding at elevated temperatures, as observed for supramolecular spheres generated from short helical columns of crown-like molecules.<sup>13,16</sup> Enantiomerically pure dendrons (R)-(3,4-3,4)-BpPr12G2-CONHsecBu (8) and (S)-(3,4-3,4)-BpPr12G2-CONHsecBu (9) self-assemble into  $Pm\bar{3}n$  phases only above 114 °C and hence the chirality of their cubic phases could not be investigated.

Hierarchical self-assembly of the chiral dendrons into chiral supramolecular spheres is summarized for dendron 4 in Figure 3. Approximately 140 molecules of 4 self-assemble to form a supramolecular sphere (Figure 3a). The projection of the solid angle ( $\alpha' = 360^\circ/\mu$ , where  $\mu$  is the number of dendrons in the supramolecular sphere)<sup>17</sup> indicates that each molecule of 4 adopts a conical conformation with  $\alpha' \approx 2.6^\circ$  (Figure 3b). The molecular length (54 Å), determined by molecular modeling,



**Figure 3.** Self-assembly of a chiral sphere of dendron 4. (a) Molecular structure of 4. Experimental densities enable calculation of the average number of molecules in a supramolecular sphere in the  $Pm\bar{3}n$  phase. (b) Conical conformation of 4 represented in (top) CPK, (center) stick, and (bottom) schematic 3D views. (c) Self-assembly of ~140 conical dendrons with chiral apex groups generate a chiral supramolecular sphere. A yellow spherical helix has been added to aid visualization of the chiral arrangement of dendrons within the sphere.

and average diameter of the supramolecular sphere (110 Å), determined from the lattice parameters determined by XRD, are consistent with a micellar-like supramolecular sphere (Figure 3c). The proposed model of supramolecular sphere of 4 comprises 140 conical molecules arranged in a spherical right-handed helix (Figure 3c). This helical sense is selected by the chiral group at the apex of the biphenylpropyl dendron, whose chirality is transferred from the chiral group to the aromatic portions of the dendrons, and then via the supramolecular sphere to the macroscopic bulk phase, as detected by CD (Figure 2). The structures of spheres assembled from third generation dendrons 6 and 7 are analogous to that of 4. In contrast, the diameter of the supramolecular sphere of 2 (150 Å) is significantly larger than twice its molecular length (60 Å), indicating that spheres assembled from 2 adopt a hollow structure, similar to that of the corresponding ester.<sup>2c</sup>

In summary, the supramolecular spheres self-assembled from conical biphenylpropyl dendrons with chiral groups at the apex have been demonstrated to be chiral. This chirality is manifested as a spherical-like helix, the helical sense of which is selected by the stereocenter at the center of the supramolecular sphere via hierarchical transfer of stereochemical information. A  $Pm\bar{3}n$  phase self-organized from chiral supramolecular spheres exhibits chiroptical activity on the macroscopic scale, as shown by CD. As the introduction of a stereocenter merely selects the handedness of an already chiral assembly<sup>2a,b</sup> rather than inducing formation of a chiral structure,<sup>18</sup> as demonstrated for helical columns by XRD,<sup>19</sup> this work raises the question of whether spheres of dendrons with methyl ester groups<sup>2c</sup> were chiral but racemic or that the



lattice is generated from mixtures or fragments of homochiral sphere.<sup>20</sup> This would imply that the incorporation of a chiral group at the apex has merely selected a single handedness, giving chirality that was detectable on the macroscopic scale (Figure 2). Unfortunately, fiber XRD cannot demonstrate in the case of spheres as in the case of columns<sup>19,20</sup> that a stereocenter selects the helical sense of an already chiral but racemic assembly. By extension, does this mean that micellar-like spheres and micelles generated from block copolymers, surfactants, and other molecules which self-organize into Frank–Kasper phases are also chiral? Furthermore, if this is the case, why do spheres elect to self-assemble in a chiral manner, how is chirality correlated between supramolecular spheres within a single cubic unit cell and how is chirality maintained and hierarchically transferred during phase transitions to and from Frank–Kasper phases, especially in systems that exhibit supramolecular orientational memory<sup>16b,c</sup> remain open questions.

## ■ ASSOCIATED CONTENT

### ■ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.9b02206.

Synthetic procedures with complete characterization data, and experimental methods (PDF)

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### Notes

The authors declare no competing financial interest.

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